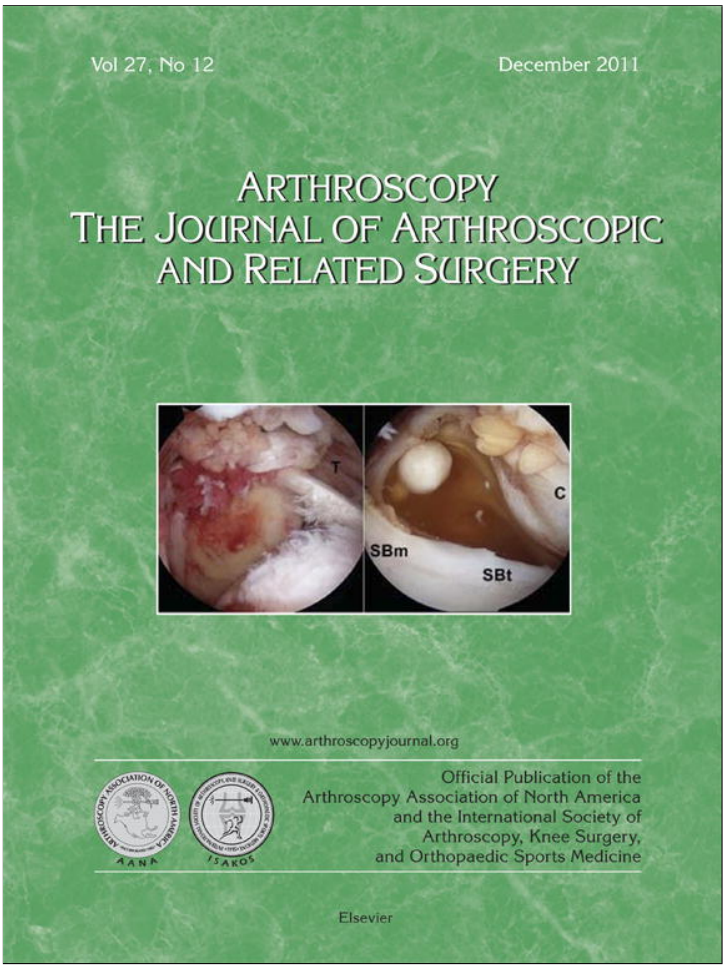

Systematic Review

Tissue Engineering and Regenerative Medicine Strategies in Meniscus Lesions

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Purpose: The aim of this systematic review was to address tissue engineering and regenerative medicine (TERM) strategies applied to the meniscus, specifically (1) clinical applications, indications, results, and pitfalls and (2) the main trends in research assessed by evaluation of preclinical (in vivo) studies. **Methods:** Three independent reviewers performed a search on PubMed, from 2006 to March 31, 2011, using the term "meniscus" with all of the following terms: "scaffolds," "constructs," "cells," "growth factors," "implant," "tissue engineering," and "regenerative medicine." Inclusion criteria were English language–written, original clinical research (Level of Evidence I to IV) and preclinical studies of TERM application in knee meniscal lesions. Reference lists and related articles on journal Web sites of selected articles were checked until prepublication for potential studies that could not be identified eventually by our original search. The modified Coleman Methodology score was used for study quality analysis of clinical trials. **Results:** The PubMed search identified 286 articles (a similar search from 2000 to 2005 identified 161 articles). Non–English-language articles (n = 9), Level V publications (n = 19), in vitro studies (n = 118), and 102 studies not related to the topic were excluded. One reference was identified outside of PubMed. Thirty-eight references that met the inclusion criteria were identified from the original search. On the basis of our prepublication search, 2 other references were included. A total of 9 clinical and 31 preclinical studies were selected for further analysis. Of the clinical trials, 1 was classified as Level I, 2 as Level II, and 6 as Level IV. Eight referred to acellular scaffold implantation for partial meniscal replacement, and one comprised fibrin clot application. The mean modified Coleman Methodology score was 48.0 (SD, 15.7). Of the preclinical studies, 11 original works reported on studies using large animal models whereas 20 research studies used small animals. In these studies the experimental design favored cell-seeded scaffolds or scaffolds enhanced with growth factors (GFs) in attempts to improve tissue healing, as opposed to the plain acellular scaffolds that were predominant in clinical trials. Injection of mesenchymal stem cells and gene therapy are also presented as alternative strategies. **Conclusions:** Partial meniscal substitution using acellular scaffolds in selected patients with irreparable loss of tissue may be a safe and promising procedure. However, there is only 1 randomized controlled study supporting its application, and globally, many methodologic issues of published trials limit further conclusions. We registered a different trend in preclinical trials, with most considering augmentation of scaffolds by cells and/or GFs, as opposed to the predominantly acellular approach in clinical trials. Different TERM approaches to enhance meniscal repair or regeneration are in preclinical analysis, such as the use of mesenchymal stem cells, gene therapy, and GFs alone or in combination, and thus could be considered in the design of subsequent trials. **Level of Evidence:** Level IV, systematic review of Level I to IV studies.

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The advent of tissue engineering (TE) promises to revolutionize the concept of medicine by using strategies mimicking the mechanisms underlying normal tissue formation and regeneration. As stated by Langer and Vacanti,[1] TE is the field of research that envisions the use of both "principles of engineering and life sciences towards the development of biological substitutes to restore, maintain, or improve tissue function." TE strategies, by definition, make use of 3 main variables, that is, scaffolds, cells (differentiated or undifferentiated), and bioactive agents or growth factors (GFs), that can be implanted into the damaged site, alone or in combination. On the other hand, regenerative medicine is a wider concept, and besides comprising the use of soluble molecules and stem cell technology, it also can apply TE and gene therapy strategies to restore or establish normal functions of cells/tissues/organs. Given the pivotal roles of the meniscus in knee homeostasis and proper joint function/stability, the development of regenerative treatments as an alternative to meniscectomy or traditional repair procedures has been attempted.

"Nothing has changed so much in knee treatment and surgery as the meniscal treatment algorithms." This statement from René Verdonk[2] perfectly summarizes the overturn that has occurred in the approach toward meniscus lesions in recent years. The wedge-shaped semilunar disks of fibrocartilaginous tissue that characterize menisci play critical roles in knee joint biomechanics. In fact, it has been recognized that their removal determines deleterious joint consequences, particularly in the long-term.[3,4]

The biologic characterization of meniscus tissue, though not yet completely accomplished, has evolved significantly in the last few years. This is true concerning recognition of different cellular populations, understanding its ultrastructure,[5] cells and extracellular matrix segmental distributions, biomechanical properties, biologic interactions, or injury response mechanisms.

The need for meniscal repair/regeneration is increasingly appreciated, with growing calls appealing for the need to "save the meniscus."[6] When repair is no longer possible, substitution seems to be the most adequate answer,[7] with growing experience and consensus around meniscal allograft transplantation for whole meniscal replacement in selected cases. Moreover, meniscal lesions, in their various forms, subsist as 1 of the most frequent injuries leading to orthopaedic surgery.[8] Considering the significant socioeconomic impact and the scarcity of reliable clinical solutions, it is evident that meniscal repair urgently requires the development of new effective strategies.[8]

The general clinical community (orthopaedic surgeons included) has increasingly recognized the relevance of basic science and tissue engineering and regenerative medicine (TERM)–related research[9] in opening up a new world of perspectives to deal with some health-related problems. Being that meniscal repair/regeneration is a hot topic in orthopaedics and, more recently, in the field of TERM, the great advances in meniscal research should be reviewed to fully comprehend its progress and potential impact on clinical practice.

The purpose of this review is to summarize the hierarchy of studies dealing with TERM strategies applied to the meniscus while providing a systematic narrative that will enable clinicians/experts to become familiar with the most recent developments in this field. Thus we review relevant information related to (1) clinical applications, indications, results, and pitfalls and (2) the main research directions in the field of meniscal repair/regeneration assessed by evaluation of preclinical (in vivo) studies.

Besides establishing the state of the art of clinical application within this topic, we aim to summarize relevant preclinical information, thus facilitating the final step of translating research from bench to bedside in the nearby future and helping the "recently recognized" orthopaedic clinician-scientists[10,11] in designing valid research projects.

METHODS

Three independent reviewers performed a search on PubMed for original works published from 2006 to March 31, 2011, using the term "meniscus" with all of the following terms: "scaffolds," "constructs," "cells," "growth factors," "implant," "tissue engineering," and "regenerative medicine." A second search period (2000 to 2005) was considered to assess the evolution of interest in this topic reflected in the number of publications.

Inclusion criteria were the following: English language–written, original clinical and preclinical (in vivo) studies of TERM application in knee meniscal lesions published from 2006 to March 2011. All abstracts were evaluated; only Level I to IV clinical studies were considered.

The full-text article was reviewed; reference lists and related electronic libraries checked until prepublication period for screening relevant studies that could not be identified eventually by our original

Table 1. *Summary of Search Strategy, Exclusion Criteria, and Evidence Level of Identified Articles*

Initial search terms from 2000 to 2005	161
Initial search terms from 2006 to 2011	286
Exclusion of studies not related to topic (or not proposing specific approach to meniscus)	102
Exclusion of non–English-language studies	9
Exclusion of in vitro studies	118
Level V studies (case report, authors' opinion, nonsystematic review)	19
References not identified by PubMed	1
Clinical (Level I-IV) studies included based on original search	8
Preclinical (in vivo) studies included based on original search	30
Articles identified from prepublication search (preclinical and clinical)	2

search. Articles were classified by levels of evidence, according to the 5-level system.[12] Clinical studies' quality analysis was assessed with the Coleman Methodology score as modified by Kon et al.[13] In addition, preclinical studies were also considered to assess promising research trends aiming for clinical application. All articles identified by these search terms were manually reviewed and discussed among us, and a decision was made regarding inclusion or exclusion. In the absence of agreement among us, the final decision was made by the senior author (R.L.R.).

RESULTS

By use of the described method in the period 2000 to 2005, 161 articles were identified, whereas from 2006 to March 2011, this number increased to 286 (Table 1). From the last group of articles (n = 286), 102 were excluded because they were classified as not specifically addressing the topic. In addition, non–English-language articles (n = 9) and Level V publications (n = 19) were eliminated. No previous systematic review was found relating this topic. Early-stage in vitro studies (n = 118) dealing with cell culturing and cytotoxicity screening of materials were also excluded. One reference was identified by checking reference lists and searching in related libraries or journal Web sites. Considering the inclusion and exclusion criteria, we identified and selected 38 references[14-51] from the original search for further analysis. Two other relevant references were identified by the prepublication search[52,53] (Table 1).

Clinical Studies Using TE Strategies for Meniscus Regeneration

For the clinical trials, we identified 1 as Level I,[36] 2 as Level II,[29,47] and 6 as Level IV.[16,20,22,46,51,52] Table 2 summarizes the clinical experience studies involving the treatment of injured or degenerated meniscus. The mean modified Coleman Methodology (MCM) score for all TERM strategy trials was 48.0 (SD, 15.7).

Of the 9 clinical studies, 8 actually referred to acellular scaffold implantation for partial meniscal replacement (7 collagen based and 1 polyurethane based). One of the clinical trials comprised fibrin clot application (scaffold-GF approach) as an enhancer of horizontal cleavage repair in the avascular zone.

The 7 published trials reporting on Collagen Meniscus Implant (CMI) (currently known as Menaflex; ReGen Biologics, Hackensack, NJ) application enrolled 565 patients; 487 were evaluated and 304 received CMI devices, all for medial meniscus defects. The mean MCM score of the CMI trials was 50.6 (SD, 12.6). One study compared high tibial osteotomy (HTO) alone with HTO combined with CMI.[29] Two used partial meniscectomy patients as control groups.[36,47] The remaining studies were case series without control groups (Table 2). Control subjects comprised 167 partial meniscectomies and 16 HTO procedures. The mean age reported for CMI application ranged from 29.2 years[52] to 41.8 years.[29] One of the studies did not provide any gender information,[29] but in the remaining studies, 223 were men and 61 women. The mean follow-up period ranged from 24 months[29] to approximately 133 months.[47,52] One trial reported results up to 24 months' follow-up, but no central-tendency numeric value was provided.[20]

Concomitant surgeries during CMI implantation comprised 96 anterior cruciate ligament (ACL) reconstructions,[16,20,36,47,50,52] 26 HTOs,[16,20,29] 7 microfractures,[16,20,46,47,52] and 2 autologous chondrocyte implantations[20] for chondral lesions up to grade III.

Five trials considered a division in 2 groups of candidates for the implant: (1) acute irreparable meniscal lesions and (2) a chronic arm with prior tissue loss.[16,20,36,46,47] Only 2 provided some information on meniscal tear type.[16,52] Scarce information was provided regarding previous surgeries in terms of time to index surgery and type of surgery.[36,46,52] In the study considering CMI use in HTO candidates, no information on preoperative or postoperative varus-valgus alignment was provided for either cases or control subjects.[29]

TABLE 2. *Clinical and Follow-up Studies for Treatment of Injured or Degenerated Meniscus*

Reference	Meniscal Defect	Therapeutic Approach	No. of Cases/ No. of Control Subjects	Control Group	Patient Age (Mean)	Follow-up	Image Evaluation	Second-Look Arthroscopy (Y/N)	Clinical Outcome	Level of Evidence	MCM Score
Linke et al.[29] (2006)	Partial medial meniscus defect with intact rim (not further defined)	HTO + CMI acellular	23/16	HTO alone	41.8 yr	24 mo	—	Yes (n = 23)	IKDC, Lysholm, VAS	Level II	50
Zaffagnini et al.[46] (2007)	Partial medial meniscus defect >25% with preserved peripheral rim	CMI implantation acellular	8/—	—	31.0 yr	6.8 yr	Radiography, MRI	Yes (n = 3)	CKRS, IKDC, VAS	Level IV	49
Genovese et al.[20] (2007)	Partial medial meniscus defect (not defined)	CMI implantation acellular	40/—	—	41.0 yr	24 mo	MRI	Yes (n = 12)	—	Level IV	32
Rodkey et al.[36] (2008)	Partial medial meniscus defect >25% with preserved peripheral rim	CMI implantation acellular	160/151	Partial meniscectomy	Acute, 38.0 yr; chronic, 40.0 yr	59 mo	—	Yes (n = 141)	Lysholm, Tegner, VAS	Level I	72
Bulgheroni et al.[16] (2010)	Partial medial meniscus defect >25% with preserved peripheral rim	CMI implantation acellular	34/—	—	39.0 yr	60 mo	Radiography, MRI	Yes (n = 8)	Lysholm, Tegner	Level IV	42
Zaffagnini et al.[47] (2011)	Partial medial meniscus defect >25% with preserved peripheral rim	CMI implantation acellular	17/16	Partial meniscectomy	38.0 yr	135 mo	Radiography, MRI	No	Lysholm, IKDC, Tegner, VAS, SF-36	Level II	59
Kamimura and Kimura[24] (2011)	Horizontal cleavage defect, avascular zone (medial or lateral meniscus)	Suture + autologous fibrin clots, scaffold-GF	9/—	—	Not defined	12 mo	—	Yes (n = 1)	Lysholm (n = 1)	Level IV	19
Verdonk et al.[51] (2011)	Partial meniscus defect (medial or lateral; intact rim; mean length, 47.1 mm)	Polyurethane scaffold implantation acellular	52/—	—	30.8 yr	12 mo	MRI (DCE)	Yes (n = 44) Biopsy histology (n = 44)	—	Level IV	59
Monllau et al.[52] (2011)	Partial medial meniscus defect with preserved peripheral rim (mean length, 48.2 mm)	CMI implantation acellular	25/—	—	29.2 yr	133.2 mo	Radiography, MRI	Yes (n = 2)	Lysholm, VAS	Level IV	50

Abbreviations: DCE, dynamic contrast enhanced; VAS, visual analog scale; IKDC, International Knee Documentation Committee; CKRS, Cincinnati knee rating scale; SF-36, Short Form 36.

The time interval between injury, onset of symptoms, or prior meniscectomy surgeries and implantation was poorly defined or not defined at all.

Several different clinical scoring systems were used. In decreasing order of frequency, these were the Lysholm score (n = 5),[16,29,36,47,52] subjective visual analog scale for pain (n = 5),[29,36,46,47,52] Tegner activity level score (n = 3),[16,36,47] International Knee Documentation Committee objective form (n = 2)[46,47] and subjective form (n = 1),[29] Cincinnati knee rating scale (n = 1),[46] and Short Form 36 score (n = 1).[47] The preoperative Tegner score was based on patient recall in 2 trials.[36,47] One study using magnetic resonance imaging (MRI) evaluation did not present clinical outcome.[20] Besides this variety, scarce numeric data presentation (including lack of or scarce statistical dispersion measure presentation) for descriptive statistics and clinical outcome in all trials limited global outcome analysis.

Four studies included independent radiographic evaluation[16,46,47,52]: one used the Kellgren-Lawrence score,[16,46] another compared joint space narrowing of the operated knee with the healthy contralateral knee,[47] Monllau et al.[52] used the Ahlbäck classification, and no specific method was referred to in the fourth.[46]

MRI evaluation was reported in 5 trials.[16,20,46,47,52] Genovese et al.[20] described an MRI score of 1 to 3 degrees, where a higher score more closely resembles the normal meniscus considering morphologic and signal features. This was used in 3 subsequent studies.[16,47,52] Genovese et al. also proposed MRI arthrography evaluation for better chondral lesion assessment (in 2 cases conventional MRI failed to distinguish chondral lesions detected only through arthrography), which was also considered by Bulgheroni et al.[16] Four trials presented results of second-look arthroscopies in a total of 187 patients.[16,20,29,46] The mean length of CMI applied was reported in 3 trials, ranging from 3.6 to 4.8 cm.[16,47,52] An increase in total tissue area, considering the existing meniscus rim at index surgery and the new tissue formed registered on second-look examination, was also described.[36] Biopsies were performed in 149 patients from 2 trials.[16,36] Despite this, no specific score or histologic objective evaluation method was used. The outcome relies mainly on visual estimates or generic conclusions of histologic evaluation without consideration of a reproducible method.

Considering failure as the inability to identify the implant on MRI, 7 cases of failure were described.[20,46,47,52] One of these was reoperated on for removal of remnants, and second-look arthroscopy confirmed the diagnosis.[20] No further considerations were provided for the others. Besides this, 6 others were removed (totaling 7): 1 for disorganization,[52] 1 for disorganization and luxation,[29] 2 for early failure[16,36] (1 patient did not comply with rehabilitation[16]), 1 for infection,[36] and 1 for unreported cause.[36]

Reoperations were needed in 8 patients because of effusion and/or pain, stiffness, locking, or instability.[36,47,52] Reoperation related to the implantation comprised 1 case of entrapment of the saphenous nerve's infrapatellar branch requiring neurolysis.[16] Thus a total of 15 of 282 patients were reoperated on for complications considered as possibly related to the described method.

Salvage procedures included arthroscopic debridement/lavage alone or in combination,[16,20,29,36,46,47] HTO,[36,47,52] ACL repair,[36] partial meniscectomy,[36] and meniscal allograft transplantation.[52]

Reduced implant size with time was reported in all trials assessed by MRI or second-look arthroscopy. However, the correct incidence of this fact was not possible to determine because it was not specifically addressed with regard to either its magnitude or its influence in the outcome.

No clinically relevant data on severe inflammation or immune response were found in any of the biopsy specimens reported on.

Only 1 multicenter, Level IV, single-armed study, with 52 patients, reports on clinical experience with a polyurethane-based implant (Actifit; Orteq, London, England).[51] There were 39 male patients and 13 female patients, with a mean age of 30.8 years (SD, 9.4 years), and 34 medial and 18 lateral meniscus lesions, with a mean longitudinal length of 47.1 mm. No clinical outcome was presented (the authors proposed to assess tissue ingrowth and safety) using independent MRI analysis (blinding to clinical data) including dynamic contrast-enhanced MRI (method to assess tissue vascularization).

Qualitative histologic analysis was presented in 44 of 52 cases. At 12 months, 1 case of no integration of the scaffold with the native meniscus was registered.

Regarding registered complications at 12 months' follow-up, a postoperative infection developed in 1 patient (1 week after index surgery, the scaffold was removed as part of the treatment); 1 patient was submitted to a total knee arthroplasty 4 months after the implant placement (considered an error of inclusion for severe osteoarthritis since the beginning); and 1 patient had a myocardial infarction. All these complications were classified as not related to the scaffold.

One trial proposed a fibrin clot approach to broaden the indication for repair of horizontal cleavage tears in avascular-zone cases.[24] The defect was filled with fibrin clots before tightening the sutures in a "sandwich fashion." This series initially reported on 3 medial and 6 lateral menisci. Generic conclusions regarding improvement in functional scores are presented, but the Lysholm score was accessible for only a single patient.

Preclinical Studies Using TE Strategies for Meniscus Regeneration

To organize data for our analysis, preclinical reports (n = 31) were grouped considering the animal model used, that is, large or small animals (Tables 3 and 4). The stream of research considers the following: strategies aiming to enhance suture repair, total or partial replacement, and percutaneous therapies to increase tissue repair or decrease degradation rate. Among the 31 preclinical studies related to this topic, 11 reports used large animal models such as swine, sheep, and goats (Table 3). From Table 3, it is possible to observe that 4 studies focused on the use of an acellular scaffold[17,30,50,53] and 6 studies used either allogeneic[41,42] or autologous[27,31,41] cells with scaffolds or scaffolds combined with GFs (vascular endothelial growth factor [VEGF]).[28,34] A gene therapy approach was also used in 1 study by combining an injectable alginate gel with transfected bone marrow cells with human insulin-like growth factor 1 (hIGF-1).[49]

Twenty studies using small animal models (e.g., mice, rats, rabbits, and dogs) were identified (Table 4). These studies were mainly focused on TE strategies comprising the use of acellular scaffolds and cell-scaffold constructs.

Combining all preclinical articles from Tables 3 and 4, it can be seen that 11 works were focused on acellular scaffold approaches,[17-19,21,30,35,39,40,44,50,53] 9 tested a cell-seeded scaffold approach,[15,25,27,31,37,41-43,45] and 2 studies tested a combination of cell-scaffold GFs,[26,49] 1 of which also used gene therapy.[49] In addition, 1 study compared cell-seeded scaffold and scaffold-GF approaches,[48] and another tested the immunocompatibility of a scaffold in vivo (decellularized porcine meniscus) but describe the intention for future cell-seeded construct approach.[38] Three studies tested a combination of scaffold-GFs,[23,28,34] 3 proposed injected mesenchymal stem cells (MSCs),[14,22,32] and 1 presented only a gene therapy approach[33] in preclinical experiments. Figure 1 illustrates the heterogeneity and the number of articles using the different treatment strategies in both clinical and preclinical studies. Whereas most clinical trials deal with acellular scaffold implantation alone for partial replacement of irreparable meniscus defect (8 of 9 studies), the same trend is not present in preclinical research works. In the latter group, most studies involving the application of scaffolds (n = 27) favor its use in combination with cells (constructs) or with GFs (16 of 27).

DISCUSSION

Most patients reported on in the clinical studies are aged in their 30s to 50s, within an age related to higher working productivity. Bearing this fact in mind, one can extrapolate important consequences in lost days at work and the relevant socioeconomic impact of meniscal lesions. In such a young population, we can commonly expect good cartilage status for stable (or stabilized) knees with meniscal lesions. Therefore this represents the ideal target to defend meniscus function to prevent early joint degeneration. The Multicenter Orthopaedic Outcomes Network (MOON), using from a large prospective cohort of relatively young patients undergoing ACL reconstruction, has concluded that there is a large potential market for meniscus-related TERM strategies through scaffolds, advancing repair to the avascular zone, or performing all-biologic repairs without implants.[54] For all the aforementioned reasons, this is a subject requiring attention from the knee-surgeon community, and significant socioeconomic impact can be expected from cost-effective strategies in this area. Certainly, this requires mastering a new field of knowledge and its specific language. Development of new TERM trends requires the combined effort of several areas, such as clinical orthopaedics, veterinary medicine, biochemistry, biology, and TE or regenerative medicine, but assessing basic science reports is not always easy for clinicians. In turn, to help bring research from bench to bedside, clinicians must help develop novel strategies to organize and stratify knowledge and strengthen the bonds with basic science researchers.

Clinical Studies Using TE Strategies for Meniscus Regeneration

In all 8 clinical studies reporting on scaffold implants, we can find global consensus about indications unrelated to the material applied that we can summarize as (1) irreparable traumatic or degenerative loss of meniscus tissue with preserved anterior and posterior meniscus insertions and preserved peripheral rim; (2)

TABLE 3. *Studies of Meniscal TE Strategies Used in Large Animal Models (Sheep, Goats, and Swine)*

Reference	Animal Model (Defect)	Therapeutic Approach	Scaffolds	Cells	GFs	Controls	Characterization Techniques*
Weinand et al.[41] (2006)	Swine (bucket-handle lesion in medial menisci)	Cell-scaffold construct (autologous or allogeneic scaffold)	Woven Vicryl mesh PLGA	Autologous and allogeneic swine chondrocytes (articular, auricular)	—	Unseeded mesh, suture, empty defect	d
Weinand et al.[42] (2006)	Yorkshire swine (meniscal partial defect–avascular anterior middle region of medial meniscus, 1-cm bucket-handle lesion)	Cell-scaffold construct (allogeneic scaffold)	Woven Vicryl mesh PLGA	Allogeneic swine chondrocytes (articular, auricular, costal)	—	Sutured unseeded mesh, suture, empty defect	a, c, d
Martinek et al.[31] (2006)	Merino sheep (meniscus resection); 3 cm of Achilles tendon was simultaneously removed	Cell-scaffold construct (autologous scaffold)	CMI	Autologous meniscus fibrochondrocytes	—	Unseeded CMI, empty defect	a, c, d
Chiari et al.[17] (2006)	Austrian stone sheep, total (medial meniscectomy) or partial defects (resection of anterior portion)	Acellular scaffold	Hyaluronic acid (HYAFF)–polycaprolactone	—	—	Empty defect	a, d
Petersen et al.[34] (2007)	Merino sheep (15-mm longitudinal tears)	Scaffold-GF	PDLLA-coated sutures	—	VEGF	PDLLA sutures, uncoated sutures (Ethibond No. 2-0; Ethicon)	a, d, e
Kon et al.[27] (2008)	Bergamasca-Massese and Austrian stone sheep (total meniscus defect)	Cell-scaffold construct (autologous scaffold)	Hyaluronic acid (HYAFF)–polycaprolactone	Autologous articular chondrocytes	—	Acellular scaffold	a, b, c, d
Zhang et al.[49] (2009)	Chuandong white goats (partial defect, 3 mm in diameter in medial menisci)	Cell-scaffold-GF construct (gene therapy)	Calcium alginate gel (injectable)	Transfected hIGF-1 BM-MSCs	—	Gels with BM-MSCs (not transfected, calcium alginate gel, empty defect	a, b, d, e, h
Kopf et al.[28] (2010)	Merino sheep (partial, 15-mm longitudinal tears in medial menisci)	Scaffold-GF	PDLLA-coated sutures	—	$VEGF_{165}$	PDLLA sutures, uncoated sutures (Ethibond No. 2-0)	a, d, e, g
Maher et al.[30] (2010)	Columbia X Rambouillet sheep (partial defect)	Acellular scaffold	Polyurethane based	—	—	Empty defect	a, d, h
Zur et al.[50] (2011)	"Asaph" sheep (total medial meniscectomy)	Acellular scaffold	Kevlar fibers–polycarbonate–urethane	—	—	Unoperated healthy knees	a, d
Galley et al.[53] (2011)	Columbia X Rambouillet sheep (partial defect)	Acellular scaffold	Polyurethane based	—	—	Normal tissue	a, d, f

Abbreviations: BM, bone marrow; PLGA, poly(lactic-co-glycolic acid).
*The techniques were as follows: a, macroscopic analysis; b, electron microscopy analysis; c, animal clinical evaluation; d, histologic analysis; e, immunohistochemistry; f, biomechanical analysis; g, polymerase chain reaction; and h, MRI evaluation.

TABLE 4. *Small Animal Models (Mice, Rats, Rabbits, and Dogs) Using TE Strategies for Meniscus Regeneration*

Reference	Animal Model (Defect)	Therapeutic Approach	Scaffolds	Cells	GFs	Controls	Characterization Techniques*
Agung et al.[14] (2006)	Normal Sprague-Dawley (SD) rats (meniscal partial defect–avascular central area; simultaneous ACL and cartilage defects); size of defect is not reported	Injected BM-MSCs (tibia) from green fluorescent protein Sprague-Dawley rat (transgenic)	—	Bone marrow (BM-MSCs) (tibia)	—	Saline solution injection, MSCs without green fluorescent protein injected in sham-operation rats	d, e
Mizuno et al.[32] (2008)	Normal Sprague-Dawley rats (meniscal partial cylindrical anterior horn defect, 1.0 mm)	Injected synovial MSCs from green fluorescent protein Sprague-Dawley rat (transgenic)	—	Synovial MSCs	—	Phosphate-buffered saline solution injection, MSCs without green fluorescent protein injected in sham-operation rats	a, b, d, e
Yamasaki et al.[45] (2008)	Normal Sprague-Dawley rats (total defect)	Cell-scaffold construct (allogeneic scaffold)	Decellularized meniscus from rat	BM-MSCs (tibia) from green fluorescent protein Sprague-Dawley rat	—	Empty defects (meniscectomy), decellularized meniscus scaffold alone	a, d
Ochiai et al.[33] (2008)	Bach 1–deficient and wild-type C57BL/6J mice (meniscus degeneration)	Gene therapy (Bach 1–deficient mice), suppression of oxidative stress mediated by HO-1	—	—	—	Wild-type C57BL/6J mice	d, e, g
Scotti et al.[37] (2009)	Nude mice (bonding meniscus tissue slices and subcutaneous implantation)	Cell-scaffold construct (tri-layered)	Fibrin glue hydrogel	Allogeneic swine articular chondrocytes	—	10/10 subcutaneous implantation (cases: 10 constructs; controls: 10 acellular scaffolds)	a, b, d
Weinand et al.[43] (2009)	Nude mice (bonding meniscus tissue slices, subcutaneous implantation)	Cell-scaffold construct	Vicryl mesh (PLGA) surrounded by fibrin glue and decellularized meniscus surrounded by fibrin glue	Allogeneic swine chondrocytes (articular, auricular, costal) seeded under static and dynamic conditions	—	—	a, d, f
Horie et al.[22] (2009)	Wild-type male Lewis rats (anterior half of medial meniscus defect)	Injected autologous synovial MSCs	—	Autologous synovial MSCs and BM-MSCs	—	14/36 (cases: 14 right knees, s-MSCs; controls: 9 BM-MSCs, 23 left knees with phosphate-buffered saline injection; 4 normal right knees injected with s-MSCs; imaging analysis)	b, d, e, g
Stapleton et al.[38] (2011)	Galactosyltransferase knockout mice (host response to scaffold subcutaneous implantation)	Scaffold acellular, cell-scaffold construct	Decellularized porcine meniscus	Porcine medial meniscal cells	—	Vaccinated and nonvaccinated fresh porcine meniscus, α-galactosidase–treated porcine meniscus	d, e
Kang et al.[25] (2006)	New Zealand white rabbits (total meniscus defect)	Cell-scaffold construct	Polyglycolic acid mesh physically bonded with 75:25 PLGA	Allogeneic meniscus cells (rabbit)	—	Scaffold without cells, healthy rabbits for normal tissue control	d, e, f
Angele et al.[15] (2008)	New Zealand white rabbits (partial medial meniscus defect, 5 mm)	Cell-scaffold construct	Hyaluronan/gelatin composite scaffold	Autologous BM-MSCs	—	Empty defect, scaffold without cells, healthy rabbits for normal tissue control	a, b, d, e
Ishida et al.[23] (2007)	Japanese white rabbits (partial defect–avascular area, 1.5 mm in diameter)	Scaffold-GFs	Gelatin hydrogel (GH)	—	PRP	Total of 18 animals (cases: 12 knees with GH + PRP; controls: 12 knees with GH + PPP, 12 knees with GH alone)	d
Reckers et al.[35] (2009)	New Zealand albino rabbits (fixation of whole meniscus implant)	Scaffold acellular	Fibrin glue (Beriplast; Aventis Behring do Brasil), octyl-cyanoacrylate adhesive (Dermabond; Ethicon, São Paulo, Brazil)	—	—	Mononylon sutures	a, c, d
Zellner et al.[48] (2010)	New Zealand white rabbits (avascular meniscal defects, 2 mm)	Cell-scaffold constructs with cells from different source and cultured in vitro under different conditions, scaffold-GFs	Hyaluronan-collagen composite matrices	Bone marrow (MSCs)	PRP	Empty defect, scaffold without cells	a, b, d, e
Kobayashi et al.[26] (2010)	Japanese white rabbits (partial meniscus defect, anterior one-third)	Cell-scaffold constructs; scaffold-GFs	Meniscus fragments wrapped with fascia sheaths, use of No. 3-0 polyester sutures	Autologous meniscus cells	Autologous local GFs	Empty defect, fascia sheath alone	a, d, f

TABLE 4. *Continued*

Reference	Animal Model (Defect)	Therapeutic Approach	Scaffolds	Cells	GFs	Controls	Characterization Techniques*
Tienen et al.[40] (2006)	Beagle dogs (total lateral meniscus defect)	Scaffold acellular	Aromatic 4,4-diphenylmethane diisocyanate–based polyester urethane (Estane) and aliphatic 1,4-butane diisocyanate–based polyester urethane (PCLPU)	—	—	Estane implant, n = 6; PCLPU implant, n = 6; meniscectomy alone, n = 6	a, c, d
Tienen et al.[39] (2006)	Beagle dogs (total lateral meniscus defect)	Scaffold acellular	Polyurethane-based Estane	—	—	n = 24 knees (cases: 12 knees with Estane implant; controls: n = 12 knees with meniscectomy alone)	a, c, d, f, h
Cook et al.[19] (2006)	Mongrel dogs (partial medial meniscus defect, cut template was 10 mm in longitudinal length and 5 mm in radial depth)	Scaffold acellular	Porcine SIS	—	—	Cases: n = 29 with SIS implant; controls: n = 22 with meniscectomy alone	a, c, d, f
Cook and Fox[18] (2007)	Dogs (medial meniscus; anterior and posterior avascular area tears, 5 mm)	Scaffold acellular	PLLA conduit (central channel for fibrin clot and cells)	—	—	n = 50 tears (cases: n = 29 with PLLA conduit; controls: n = 21 with trephine alone)	a, c, d, f
Welsing et al.[44] (2008)	Beagle dogs (total lateral meniscus defect)	Scaffold acellular	PCLPU implant	—	—	Cases: n = 13 (knees with Estane implant); controls: n = 7 with meniscectomy alone, n = 6 with no surgery	a, c, d, f
Hannink et al.[21] (2011)	Beagle dogs (total lateral meniscus defect)	Scaffold acellular	PCLPU implant	—	—	Cases: n = 13 with PCLPU implant; controls: n = 7 with meniscectomy alone, n = 6 with intact meniscus	a, d, e, h

Abbreviations: BM, bone marrow; GH, gelatin hydrogel; HO-1, heme oxygenase 1; PCLPU, polycaprolactone-polyurethane; PLGA, poly(lactic-co-glycolic acid); PLLA, polylactic acid; PPP, platelet-poor plasma; SIS, small intestinal submucosa; s-MSCs, synovial mesenchymal stem cells.

*The techniques were as follows: a, macroscopic analysis; b, electron microscopy analysis; c, animal clinical evaluation; d, histologic analysis; e, immunohistochemistry; f, biomechanical analysis; g, polymerase chain reaction; and h, histomorphometry.

biologically young patients; and (3) stable or surgically stabilized knees. Similarly, we can do the same for exclusion criteria: (1) posterior cruciate ligament insufficiency of the involved knee; (2) advanced unicompartmental or global degenerative cartilage disease in the affected joint; (3) uncorrected axial misalignment in the lower extremity; (4) inflammatory arthritis or autoimmune diseases; and (5) active infection or neurologic conditions that would limit rehabilitation compliance. In controlled studies control subjects who had undergone partial meniscectomy followed a different rehabilitation program than implanted patients,[29,36,47] and this was not clearly defined for HTO patients.[29] This fact might influence short-term outcome, but we do have to agree with previous researchers that this is probably irrelevant with longer follow-up.[47] From our analysis, we could not conclude which control subjects were best suited to evaluate partial meniscal replacement strategies, that is, partial meniscectomy or HTO patients.

The variety of clinical scores used and paucity of numerical data provided impaired global assessment of results. This issue should be considered in subsequent trials.

All studies considering Menaflex/CMI presented some degree of outcome improvement compared with preoperative status.[16,20,29,36,46,47,52] Compared with HTO alone, Linke et al.[29] found no significant differences. Zaffagnini et al.[47] and Rodkey et al.,[36] using partial medial meniscectomy (PMM) controls, could not establish significant differences for Lysholm scores. Considering pain in CMI cases, 1 study could not find significant differences,[36] but significantly lower scores have been reported elsewhere.[47]

A new tool for outcome, the Tegner index (TI), was proposed by Rodkey et al.[36] (used also in 1 subsequent study[47]) in an attempt to assess the percentage of activity level loss that was regained as a result of treatment. It is calculated by subtracting the preoperative Tegner score from the latest score and then dividing this difference by the result of subtracting the preinjury score from the preoperative score. Significant improvement in the TI was noticed in the series of Zaffagnini et al.[47] and in the chronic arm but not in the acute group at latest follow-up in the trial of Rodkey et al. Besides these 2 studies,[36,47] we could not identify any other report validating TI as a measurement tool for the amount of activity loss that was regained after the procedure. Furthermore, in these trials preoperative Tegner score was based on patient recall, and thus an inherent bias must be considered.

The score described by Genovese et al.[20] for MRI evaluation has subsequently been used, facilitating

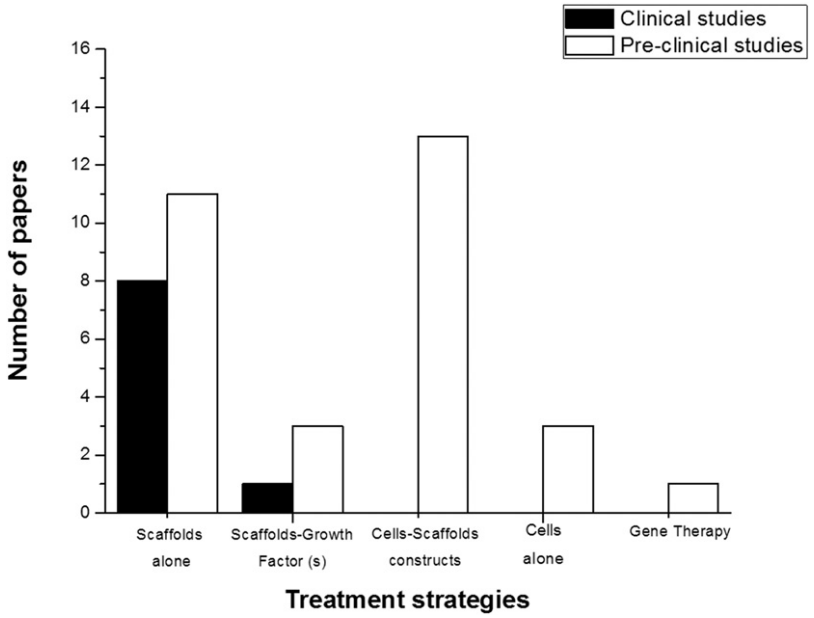

Figure 1. Number of published articles using different treatment strategies in both clinical and preclinical studies.

global analysis. The new tissue seems to mature progressively over time. However, basic features and volumetric characteristics of the obtained tissue comprise a critical issue once poorly understood.

Biopsies have been described based on generic estimates. Objective histologic evaluation topics capable of being reproduced among series would be useful. The new tissue obtained was described as not pure fibrocartilage but a hybrid repair tissue with some similarities.[36]

Early failure of implants because of dislocation or resorption has been reported, although infrequently. A decrease in the size of the implant to some extent was often reported, even if the implication in terms of clinical outcome remains unclear. Some concerns about initial lower mechanical properties have also been reported.[45]

Another consistent finding from all trials is the absence of a specific clinically relevant inflammatory or immune response to the scaffold. The only study reporting on polyurethane-based implant (Actifit) application intended to assess whether the implant is biocompatible, biomimetic, and biodegradable, in addition to its safety profile.[51] However, no clinical outcome was provided.

The length and characteristics of treated defects are similar to available data regarding the CMI. The inclusion of dynamic contrast-enhanced MRI (method to assess tissue vascularization) produced interesting data, which could possibly also be used to evaluate and compare with CMI (time and quality of integration). Qualitative histologic analysis was available for 84.6% of cases. Descriptive histologic results considering vascularization, cells, and extracellular matrix (ECM) are provided. This includes a vascularized fibrous capsule and 3 distinct layers. These results should also be considered in subsequent studies. One case of early failure was reported, but similarly, no relevant immune or inflammatory rejection was registered.

Despite positive MRI and histologic features, clinical outcomes from randomized controlled trials are needed before widespread application. Furthermore, the availability of 2 such different scaffolds intended for similar indications requires future clinical comparison between them.

Using a completely different TERM approach, Kamimura and Kimura[24] reported on their clinical experience with an original method aiming to spread the indication of meniscal lesions to horizontal tears in the avascular zone. Besides inherent innovation, finding theoretic support from basic science and having been classified originally as a Level IV study, this report should be considered a Level V report because of the paucity of objective clinical outcome data (MCM score, 19).

Preclinical Studies Using TE Strategies for Meniscus Regeneration

TERM strategies aiming to enhance suture repair, partial or total replacement of meniscus by use of

scaffolds alone or in combination with cells and/or GFs, and minimally invasive techniques to deliver engineered cells have been addressed in in vivo models, as shown in Tables 3 and 4.

With respect to TERM strategies aiming to enhance suture repair, Weinand et al.[41,42] present an implantable biodegradable construct consisting of woven Vicryl mesh (Ethicon, Somerville, NJ) seeded with either allogeneic[42] or autologous[41] chondrocytes from different tissues (articular, auricular, or costal). In their work, it was hypothesized that combining a scaffold with cells would favor suture of meniscal lesions in the avascular zone.[42] They further concluded that the presence of both autologous and allogeneic chondrocytes enhances meniscal healing in a swine model.[41] Another possibility to solve analogous problems has been reported by Petersen et al.[34] The local application of VEGF through poly-(D,L-lactide) acid (PDLLA)–coated sutures was proposed. Despite the evidence that VEGF can significantly stimulate blood vessel proliferation and healing of tears in the avascular zone of the menisci, this study showed that the local application of VEGF through PDLLA-coated sutures failed to promote meniscus healing in Merino sheep. More recently, Kopf et al.,[28] testing similar conditions, achieved analogous conclusions, raising the explanation that PDLLA is probably inadequate as a carrier. Cook and Fox[18] proposed a polylactic acid conduit with a central channel intended for fibrin clot and cell carrier application. Their results suggest that such an implant increases healing compared with trephination plus suture alone. Another study tested 2 different possibilities for fixation of meniscal allograft in rabbits: fibrin glue and octyl-cyanoacrylate.[35] It was observed that fibrin glue is not effective for fixation as compared with suture and cyanoacrylate. Whereas suture and octyl-cyanoacrylate adhesive have shown a good performance for fixation, cyanoacrylate was inadequate for the proposed application because of the severe inflammatory response.

TERM strategies aiming at total or partial replacement of the meniscus have been exploited. Chiari et al.[17] proposed a hyaluronic acid (HYAFF; Fidia Advanced Biopolymers, Abano Terme, Italy)–polycaprolactone scaffold with promising initial results for meniscal repair and substitution. Using a similar scaffold, Kon et al.[27] have shown that constructs with autologous chondrocytes seem to improve results. Actually, the presence of a cartilaginous matrix in the cell-seeded scaffolds was observed, but no cartilaginous matrix was present in the cell-free scaffolds. More recently, Zur et al.[50] proposed a nondegradable, acellular, Kevlar (E. I. DuPont de Nemours and Co., Wilmington, DE) reinforced polycarbonate-urethane (PCU)–based scaffold. This work showed that the artificial meniscal implant delayed or even prevented osteoarthritic changes in the knee joint after total medial meniscectomy, thus supporting the idea that replacement of the whole meniscus can raise different issues compared with partial meniscal defects alone.

Yamasaki et al.,[45] using cell-seeded rat decellularized meniscus scaffolds, concluded that constructs are more effective than scaffolds alone. Similarly, Kang et al.[25] experimented with constructs using polyglycolic acid scaffold in rabbits and found that regeneration of the whole meniscus was possible by the TERM approach.

Tienen et al.[40] found that polycaprolactone-polyurethane evokes less tissue reaction than Estane (BF Goodrich Chemical N.V., Westerlo-Oevel, Belgium) for acellular polyurethane-based meniscus implants. These implants permitted tissue infiltration and differentiation resembling the native meniscus but were not capable of preventing cartilage degeneration. The authors further stated the need for improvement of the mechanical properties of their implants when intended for total replacement. Welsing et al.,[44] using a beagle dog model as in the former study, showed that acellular polycaprolactone-polyurethane implants also could not avoid joint degradation.

Partial replacement raises an inherently different challenge. Martinek et al.,[31] using collagen-based meniscus implant for partial replacement, concluded that constructs with autologous fibrochondrocytes perform better than CMI alone. Similarly, Angele et al.[15] found that hyaluronan/gelatin composite scaffolds seeded with stem cells perform better than empty scaffolds and represent a valuable possibility aiming at repair of meniscus defects.

A different approach aims to enhance scaffolds associated with GFs. Ishida et al.[23] described that combining gelatin hydrogel with platelet-rich plasma (PRP) as the carrier increased healing of meniscus defects compared with either of them in isolation.

Considering the TERM triad, 1 study[46] tested the use of scaffold-GFs and cell-seeded scaffolds.[48] Zellner et al.[48] compared the outcomes of PRP, hyaluronan-collagen scaffold, and bone marrow as graft harvested from the iliac crest of New Zealand white rabbits. They concluded that neither bone marrow alone nor PRP has an improved healing capacity relating to acellular scaffold. However, bone marrow–MSC constructs performed better in terms of healing and integration[48] as compared with all the previously men-

tioned constructs. A different approach providing cells and scaffold and including GFs was proposed by Kobayashi et al.[26] using meniscus fragments wrapped with fascia sheaths, with promising results.

Nevertheless, acellular polyurethane scaffold in partial defects is also capable of promoting tissue ingrowth and protecting cartilage, as concluded by Maher et al.[30] In a dog model of large defects, Cook et al.[19] verified that acellular scaffold based on porcine small intestinal submucosa provides better results than meniscectomy. Scotti et al.[37] showed the capacity of fibrin gel embedded with articular chondrocytes to increase bonding of meniscal tissue, providing initial stability and permitting cell proliferation and differentiation. Weinand et al.[43] have evaluated a dynamic oscillating cell-seeding technique in porous poly(lactic-co-glycolic acid) scaffolds with subcutaneous implantation in rats. This work has shown that auricular chondrocytes presented qualitatively better integration into native meniscus tissue than articular and costal cell implants. Stapleton et al.[38] tested the immunocompatibility profile of acellular porcine medial meniscus for cell-based TERM applications, with promising results. Despite the interesting results, a major problem in meniscus total replacement remains unsolved; that is, the need to stabilize or improve fixation of meniscus polymeric implants still exists.

TERM strategies aiming at percutaneous tissue repair/decreasing tissue degeneration have also been attracting a great deal of attention. Injectable therapies to achieve minimally invasive clinical application is an attractive and promising technology. Zhang et al.[49] investigated whether bone marrow stromal cells transfected with the hIGF-1 gene encapsulated in calcium alginate gel could improve the repair of full-thickness meniscal defects in the avascular zone of the anterior horn. The results support the efficacy of this approach to deliver biologically effective concentrations of hIGF-1 and suggested the value of liposome-mediated ex vivo gene therapy for improving meniscus healing. Injected synovial MSCs also can promote meniscal repair without mobilization to distant organs as shown by Horie et al.[22] and Mizuno et al.[32] Similarly, Agung et al.[14] tested a bone marrow–MSC injection approach for treating meniscal partial defects. MSCs were obtained from green fluorescent protein Sprague-Dawley rats (transgenic). The researchers proposed that MSC injection might be a valuable option for repair of intra-articular injuries including meniscus injuries. A completely different advanced regenerative medicine perspective is presented by Ochiai et al.[33] aiming to reduce histologic meniscus degeneration. Heme oxygenase 1 isozyme is known to mediate oxidative stress and is negatively influenced by Bach 1 transcription factor. Their study shows increased antioxidant activity in Bach 1–deficient mice resulting in diminished meniscus degeneration, thus suggesting a new stream for research aiming to prevent osteoarthritis.

Our Opinion (Level V Evidence)

When the meniscus is damaged, spontaneous healing is rare and surgery is often required. Treatment of meniscus lesions has been mainly limited to meniscectomy or partial repair by means of suturing in the vascular zone. In the last few years, we have assisted in making promising advances in the field of biomaterials and TERM. These breakthroughs have been so disrupting that they can influence common medical practice. Advanced regenerative solutions comprise the use of stem cells and are currently impacting our lives in a way never thought possible. Whereas most clinical studies dealing with meniscal repair involve the use of implants alone, such as Menaflex and Actifit, there is a growing interest in the assessment of regenerative strategies based on cell-scaffold approaches in preclinical studies. Despite the difficulty in translating such strategies to the clinical arena, the use of cells or GFs combined with polymeric scaffolds is now being envisioned and is under intensive research. Thus it is our firm belief that future clinical trials involving treatment of meniscus lesions will be designed to contemplate the use of autologous cells (e.g., stem cells) and GFs (e.g., PRP).

CONCLUSIONS

Interest in the literature on this subject is increasing, but this is the first systematic review concerning TERM clinical application and in vivo research for the treatment of meniscus defects. Partial meniscal substitution by acellular scaffolds such as polyurethane and collagen meniscus implants can be considered a safe procedure in selected patients with irreparable loss of tissue, with promising results. However, at present, most preclinical studies are pointing out some advantages to the enhancement of scaffolds with diverse cells, GFs, or both. Different TERM approaches to increase repair and tissue replacement and minimally invasive technologies including gene therapy are in preclinical analysis, opening up other clinical possibilities in the near future.

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